Clinical Applications of ASL methods

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Past and future
Fifteen years arterial spin labeling MRI has been around (1). Several issues have delayed the application of arterial spin labeling in clinical MR protocols. However, most of these issues have been solved. First of all, the quality of the arterial spin labeling MR images has been improved due to higher field strengths magnets (3.0Tesla) and optimized protocols (2,3). The interpretation of the images has become easier, with arterial spin labeling methods that are less sensitive to transit time effects, and more sensitive to cerebral blood flow. Parallel to this, radiologists have become more familiar with the interpretation of hemodynamic measurements. Furthermore, arterial spin labeling MRI has demonstrated its unique capacity to show flow territories of individual brain feeding arteries in addition to regional CBF measurements. Moreover, with the recent discussions about the safety of contrast agents the interest in the completely non-invasive arterial spin labeling method has further increased.

Technique of Arterial spin labeling
Arterial spin labeling MRI uses magnetically labeled blood as an endogenous contrast agent. With arterial spin labeling MRI, the protons of arterial water are magnetically labeled in the feeding vasculature of the brain. The labeled arterial protons flow through the vascular tree and exchange with the unlabeled brain tissue water. A perfusion-weighted image can be generated by the subtraction of an image in which inflowing arterial spins have been labeled, from an image in which spin labeling has not been performed.

Clinical arterial spin labeling CBF measurements
Obvious applications of arterial spin labeling in clinical MR protocols are cerebral blood flow measurements in patients with acute or chronic cerebrovascular disease (4). In patients with acute stroke the cerebral blood flow measurements may indicate the infarct core, with severely decreased perfusion and the infarct penumbra, with decreased perfusion but still viable brain tissue. In chronic cerebrovascular disease arterial spin labeling CBF measurements show the regionally impaired hemodynamics distal to a carotid obstruction. With adequate collateral blood flow these areas may be relatively small and with a failure of compensatory mechanism the cerebral blood flow may fall below a critical level. In tumour patients arterial spin labeling measurements show areas with high perfusion and can discriminate between high and low grade tumours (5,6). Another application of arterial spin labeling are clinical MR protocols in children. Several studies have demonstrated the results of arterial spin labeling in children with for instance sickle cell disease (7). Furthermore, in patients with cognitive decline and Alzheimer's disease arterial spin labeling perfusion measurements may be used to detect early changes in regional hemodynamics before structural changes become apparent.

Clinical selective arterial spin labeling
The ability to visualize the perfusion territories in the brain is important for many clinical applications (8). Recently, selective arterial spin labeling (selective ASL) magnetic resonance imaging (MRI) has been introduced as the first non-invasive method to visualize the perfusion territories of the individual cerebral arteries. This method enables to quantify the actual contribution of individual collateral arteries to the perfusion of the brain. In the past decade, the optimization of selective arterial spin labeling MRI techniques to image the cerebral perfusion territories has resulted in numerous labeling approaches and an increasing number of clinical applications. In specific patients groups with cerebrovascular disease, such as acute stroke, large artery steno-occlusive disease and arteriovenous malformation, selective arterial spin labeling MRI provides valuable hemodynamic information when added to current MRI protocols. As a non-invasive tool for perfusion

territory measurements selective arterial spin labeling may contribute to a better understanding of the relation between the vasculature, perfusion and brain function.

Interpretation
With the us of arterial spin labeling in clinical studies, for instance in patients with a stenosis/occlusion or acute stroke, one should realize that a local increase in transit time may result in an underestimation of the CBF. Furthermore, when there is intravascular label, arterial spin labeling will give too high CBF measurements. When one is aware of these phenomena it is possible to increase the diagnostic information of the arterial spin labeling images, for instance with the measurements of arterial timing parameters with arterial spin labeling measurements at multiple delay times.

What's new in 2008 and 2009 in arterial spin labeling?
In the last years the signal-to-noise of arterial spin labeling sequences has increased due to the use of 3D sequences in addition with for instance a spiral readout and background suppression pulses. Furthermore, the recently introduced pseudo-continuous arterial spin labeling sequence gives a high signal to noise compared to especially the pulsed arterial spin labeling techniques and this sequences can be used with a standard headcoil and SAR limitations are less of a problem compared to the continuous ASL sequence.(9) The use of this sequences at a 3.0Tesla fieldstrength has increased the quality of the arterial spin labeling perfusion images to a level where arterial spin labeling can really compete and is often super in image quality compared to SPECT and PET. The improvements in SNR can also be exploited to decrease the scantime. Recently, a few studies have described arterial spin labeling MR scan protocols with a scantime less than 1 minute.(10) These in comparison with the typical scantime in the past of 4-6 minutes. These shorter scantimes for ASL sequences will make if feasible to perform arterial spin labeling MRI in acute stroke patients and to add this sequence to standard Neuo-MR scan protocols. In the acute phase of stroke, <3 hours, thusfar no large arterial spin labeling MRI studies have been reported.(11,12) However, in a recent publications the use of arterial spin labeling in large series in standard clinical practice is described, with in addition the description of the qualitative interpretation of these images in standard clinical practice. Another area which moved forward in the last year is the of arterial spin labeling CBF measurements in children, which may be an important application because it may be advantageous to avoid gadolinium injection in children or neonates.(13) Another area of research is the timing information provided by arterial spin labeling MR sequences at multiple inversion times. With multiple inversion times after the labeling information of the arterial transit time and trailing edge time can be obtained in addition to the information on CBF. These timing information provide valuable information about the quality of the CBF that arrives via collateral pathways.(14) An area with great opportunity for arterial spin labeling is the combination of arterial spin labeling CBF measurements with medication. Nowadays, more and more studies are performed to study the effect of medication on the brain by using arterial spin labeling to evaluate the effect of the medication on the regional CBF. A obvious clinical use of arterial spin labeling in this respect is to measure the cerebral autoregulatory capacity by comparing the CBF before and after an acetazolamide or CO_2 challenge. For selective arterial spin labeling new arterial spin labeling sequences have been developed which give the opportunity for selective labeling above the level of the circle of Willis.(15) The selective labeling above the level of the circle of Willis may even further enhance the pathophysiological knowledge about cerebral infarcts.

Conclusion
Added to clinical MR protocols arterial spin labeling adds valuable hemodynamc information in a variety of patient groups. The most obvious applications of arterial spin labeling CBF measurements are acute/chronic cerebrovascular disease, intracranial tumours, patients with cognitive decline and children. In a subgroup of patients, selective arterial spin labeling may be capable to replace diagnostic iaDSA.
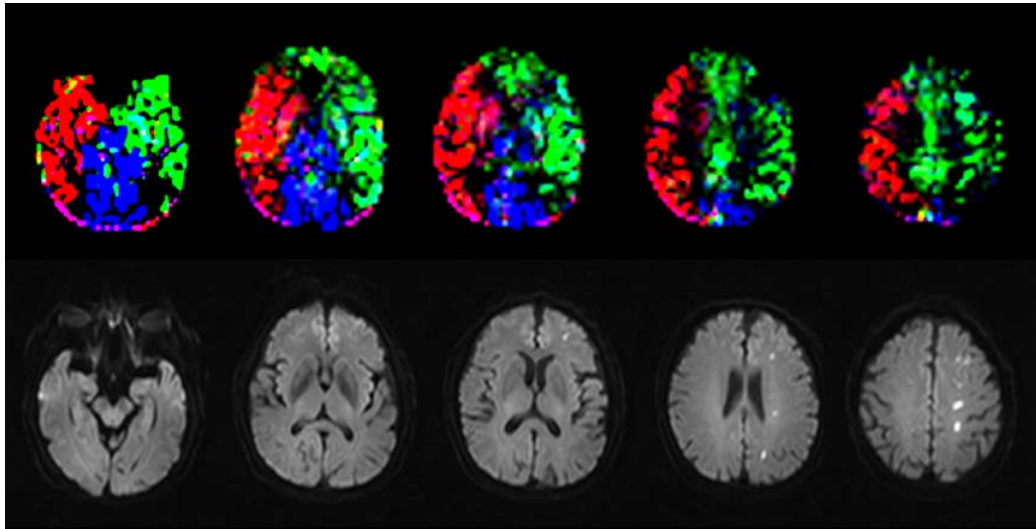
Figure 1. Perfusion territory images and corresponding diffusion weighted images (DWI) in a patient with internal border zone ischemia on the left side. Colors represent the perfusion territory of the right internal carotid artery (red), left internal carotid artery (green) and the vertebrobasilar arteries (blue). As expected the area of border zone ischemia is within the perfusion territory of the left internal carotid artery. The DWI lesion on the posterior aspect of slice 4 is located at the border of the left internal carotid artery and the vertebrobasilar artery perfusion territories, while the other lesions present in slices 4 and 5 can be estimated to fall within the internal border zone area (Hendrikse, Petersen, Golay et al. Stroke).

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